Coumarin

Coumarin (1,2-benzopyrone) has a bitter-sweet odor, and is present in tonka beans, sweet clover, lavender and citrus oils, and several other plant species. It is widely used as a fragrance in perfumes, cosmetics, personal care, and other products. It has industrial uses in the electroplating and pharmaceutical industries, and is also used to mask odors in paints, printing inks, insecticides, plastics, and synthetic rubbers. Because of its industrial uses and its many uses as a fragrance in consumer products, workers in a variety of occupations and the general public are exposed to coumarin.

Coumarin passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- 103-week gavage studies
  - Male and female B6C3F_1 mice: NTP (1993a, pp. 64, 65, 67-69, 71)
    - *Increases in combined alveolar/bronchiolar adenoma and carcinoma (by pairwise comparison and trend) and squamous-cell papilloma and combined papilloma and carcinoma of the forestomach (low-dose only) (by pairwise comparison) in males*
    - *Increases in combined alveolar/bronchiolar adenoma and carcinoma (by pairwise comparison and trend) and hepatocellular adenoma and combined hepatocellular adenoma and carcinoma (low- and mid-dose) (by pairwise comparison) in females*.
    - *Non-significant increase in combined squamous-cell papilloma and carcinoma of the forestomach in low-dose females*
  - Male and female F344/N rats: NTP (1993a, pp. 43-44)
    - *Increase in renal tubule adenoma (by pairwise comparison) in males*
    - *Non-significant increase in renal tubule adenoma in females*

- Two-year feeding studies
    - Male and female Swiss CD-1 mice: Carlton *et al*. (1996)
        - *Increase in pulmonary adenocarcinoma (by pairwise comparison) in males*
        - *Increase in combined hepatocellular adenoma and carcinoma (low-dose) (by pairwise comparison) in females*
- Two-year feeding studies (with additional *in utero* and lactational exposure via feeding of the dams in the three lowest dose groups)
    - Male and female Sprague-Dawley rats: Carlton *et al*. (1996)
        - *Increase in cholangiocarcinoma and combined hepatocellular adenoma and carcinoma (by pairwise comparison and trend) in males*
        - *Increase in cholangiocarcinoma and combined hepatocellular adenoma and carcinoma (by pairwise comparison and trend) in females*

Other relevant data

- Genotoxicity
    - As reviewed in NTP (1993a, pp. 18, 70); IARC (2000, pp. 213-216)
        - *Salmonella* reverse mutation assays, strains TA100 and TA7002 *(positive*)
        - *Salmonella* reverse mutation assays, other strains (*negative)*
        - *Drosophila melanogaster* sex-linked recessive lethal mutation assay in adults and larvae *(negative)*
        - Gene mutation assay in Chinese hamster ovary (CHO) cells *(negative)*
        - Sister chromatid exchange (SCE) in CHO cells *in vitro (positive)*
        - Chromosomal aberrations(CA) in plants *(positive)*
        - CA in CHO cells *in vitro (positive)*
        - Micronucleus (MN) formation in human hepatoma cells (*positive)*
        - MN formation in rat primary hepatocytes *(negative)*
        - MN formation in peripheral blood erythrocytes of $B6C3F_1$ mice *in vivo (negative)*
        - Unscheduled DNA synthesis (UDS) in rat tracheal epithelium cultures and human liver slices *in vitro* (*negative)*
        - UDS in rat hepatocytes *in vivo (negative)*
    - MN formation in human hepatoma cell line Hep-G2 *in vitro (positive)*: Kevekordes *et al.* (2001)
    - MN formation in bone marrow cells of Swiss mice *in vivo (negative)*: Api (2001)

- Carcinogenic activity of 3,4-dihydrocoumarin, a coumarin metabolite
    - 3,4-Dihydrocoumarin increased the incidence of renal tubule adenomas in male F344/N rats (NTP, 1993b).
    - 3,4-Dihydrocoumarin increased the incidence of liver tumors in female mice (NTP, 1993b).

- Genetic polymorphisms in the CYP2A6 gene and altered coumarin metabolism
    - The human CYP2A6 gene is polymorphic. 15–20% of Asians have a CYP2A6 gene deletion: Felter *et al*. (2006, p. 467).
    - Catalytically active forms of CYP2A6 metabolize coumarin through the 7-hydroxylation pathway, which is believed to be a detoxification pathway. Individuals with an inactive form of CYP2A6 are unable to 7-hydroxylate coumarin, and metabolism through the 3-hydroxylation pathway is observed. The 3-hydroxylation pathway leads to formation of a toxic metabolite: Hadidi *et al*. (1997).

Reviews

- IARC (2000)

References[1]

Api AM (2001). Lack of effect of coumarin on the formation of micronuclei in an in vivo mouse micronucleus assay. *Food Chem Toxicol* **39**:837-41.

Carlton BD, Aubrun J-C, Simon GS (1996). Effects of coumarin following perinatal and chronic exposure in Sprague–Dawley rats and CD-1 mice. *Fundam Appl Toxicol* **30**:145-151.

Felter SP, Vassallo JD, Carlton BD, Daston GP (2006). A safety assessment of coumarin taking into account species-specificity of toxicokinetics. *Food ChemToxicol* **44**:462-475.

Hadidi H, Zahlsen K, Idle JR, Cholerton S (1997) A single amino acid substitution (Leu160His) in Cytochrome *P*450 CYP2A6 causes switching from 7-hydroxylation to 3-hydroxylation of coumarin. *Food Chem Toxicol* **35**:903-907.

International Agency for Research on Cancer (IARC, 2000). *IARC Monographs on Some Industrial Chemicals,* Vol. 77. IARC, World Health Organization, Lyon, France. pp. 193-225.

[1] Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.

Kevekordes S, Spielberger J, Burghaus CM, Birkenkamp P, Zietz B, Paufler P, Diez M, Bolten C, Dunkelberg H (2001). Micronucleus formation in human lymphocytes and in the metabolically competent human hepatoma cell line Hep-G2: results with 15 naturally occurring substances. *Anticancer Res* **21**:461-9.

National Toxicology Program (1993a). *Toxicology and Carcinogenesis Studies of Coumarin (CAS No. 91-64-5) in F344/N Rats and B6C3F1 Mice (Gavage Studies).* Technical Report Series No. 422. NIH Publication No. 93-3153. US Department of Health and Human Services, Public Health Service, National Institutes of Health.ISS NTP-TR-382. DHHS, NIH, Bethesda MD.

National Toxicology Program (NTP) (1993b). *Toxicology and Carcinogenesis Studies of 3,4-Dihydocoumarin (CAS No. 119-84-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies).* Technical Report Series No. 423. NIH Publication No. 93-3154. U.S. Department o f Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.